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Review article

Current surface modification strategies to improve the binding efficiency of emerging biomaterial polyetheretherketone (PEEK) with bone and soft tissue: A literature review

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Abstract

Purpose: The aim of this study was to review the literature on current surface modification strategies used to improve the binding efficiency of an emerging biological material, polyetheretherketone (PEEK), with bone and soft tissues.
Study selection: This review was based on articles retrieved from PubMed, Google Scholar, Web of Science, and ScienceDirect databases. The main keywords used during the search were "polyetheretherketone (PEEK)," "implant," "surface modification," "biomaterials," "bone," "osseointegration," and "soft tissue."
Results: The suitability of PEEK surface modification strategies has been critically analyzed and summarized here. Many cell and in vivo experiments in small animals have shown that the use of advanced modification technologies with appropriate surface modification strategies can effectively improve the surface inertness of PEEK, thereby improving its binding efficiency with bone and soft tissues.
Conclusions: Surface modifications of PEEK have revealed new possibilities for implant treatment; however, most results are based on in vitro or short-term in vivo evaluations in small animals. To achieve a broad application of PEEK in the field of oral implantology, more in vivo experiments and long-term clinical evaluations are needed to investigate the effects of various surface modifications on the tissue integration ability of PEEK to develop an ideal implant material.

Keywords: PEEK, Implant, Surface modification, Osseointegration, Soft tissue

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1. Introduction

Implant treatment is a widely-used prosthodontic method used to repair dentition defects[1]. In the field of dental implants, the interface between the material and the bone or soft tissue is one of the most important research topics. Bone forms the inner foundation, while soft tissue provides external protection and performance, and implants are closely related to both[2]. Therefore, an ideal implant material should have a high binding efficiency with bone and soft tissue at the same time to form a perfect mutual relationship.

Polyetheretherketone (PEEK), a semi-crystalline polymer, has attracted much attention in the medical and biological material fields in recent decades[3]. Excellent mechanical properties, good biocompatibility, and radio permeability create conditions that allow PEEK to be used as a medical material[4,5]. PEEK medical materials have been successfully applied in orbital restoration, interbody fusion cages, artificial joints, and other applications with good clinical results[6–11].

PEEK has good aesthetic advantages owing to its white color[12], good fatigue resistance and retention, and sufficient bond strength with dental adhesive systems[13]. Therefore, PEEK shows excellent potential as a dental material. Various versions of PEEK and its composite materials, such as PEEK crowns made by CAD/CAM, retaining rings and stent materials of removable dentures, orthodontic wires, and prostheses for maxillary defects in oral and maxillofacial surgery, have also been successfully developed and applied in the field of dentistry[14–19]. The widespread use of PEEK as an oral implant material is an ongoing topic of investigation.

At present, titanium (Ti) and Ti alloys are the most common dental implant materials, but the excessively high elastic modulus of Ti (102–110 GPa) does not match that of the human bone (14 GPa)

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Table 1. Tensile strength and Young's modulus of different materials[20]

Material	Tensile strength (MPa)	Young's modulus (GPa)
PEEK	80	3-4
CF/PEEK	120	18
Ti	954-976	102-110
Enamel	47.5	40-83
Dentin	104	15
Cortical bone	104-121	14

(**Table 1**)[20], so the load cannot be evenly transmitted to the surrounding supporting tissues through the implant, resulting in "stress shielding" effects and leading to the degradation and absorption of the surrounding bone, which is not conducive to the long-term survival of the implant[21,22]. As the elastic modulus of PEEK is close to that of bone, using PEEK and its composites for bone implants can avoid the stress shielding effect caused by the difference in elastic modulus as much as possible, thereby reducing bone resorption after surgery[23]. At the same time, PEEK materials will not release metal ions or monomers incompatible with the human body, which will prevent gum allergy and mismatched coloring[24]. These advantages make it possible for PEEK to replace Ti as an implant material.

PEEK also has a few shortcomings. Its hydrophobic surface and highly reactive inertia result in low surface energy and poor biological activity[25]. These properties of PEEK can further lead to inferior osseointegration and poor adhesion between the implants and surrounding soft tissues, which severely limits its wide application in the field of implantation[26,27]. Therefore, improving the biological activity of PEEK and increasing the efficiency of its tissue integration have become the focus of attention in this field.

In view of the critical scientific problem mentioned above, the current article mainly focuses on the preparation of PEEK composite materials and their surface modifications. TiO_2/PEEK and HA/PEEK composites were prepared via melt blending using the biological activity of TiO_2 and hydroxyapatite (HA)[28,29]. Surface modifications can overcome the biological inertness of PEEK by maintaining its mechanical properties and can improve the biocompatibility, osseointegration, antibacterial, pro-vascularization, anti-tumor, immune regulation, and multiple regulation properties of PEEK materials[30].

The aim of this review was to summarize the surface modification strategies used in recent years to improve the binding efficiency of PEEK with bone and soft tissues (**Table 2**).

2. Strategies for improving the binding efficiency of PEEK with bone

The binding mechanism between an implant and bone is called osseointegration[31]. Superior osseointegration is the key to successful implant placement, whereas biological inertia on the PEEK surface delays the healing time and decreases the strength of osseointegration, leading to a decline in the success rate of implants[32]. Therefore, the goal of researchers is to improve the binding efficiency and initial stability of PEEK with bone, thereby improving the long-term success rate of implants. When biomedical materials are implanted into human bone, osseointegration efficiency is affected by their properties and surface characteristics, such as surface morphology and roughness, and chemical properties, such as hydrophilicity and hydrophobicity[33]. Current surface modification technologies can be used to implement effective strategies for modifying the surface characteristics that affect the binding efficiency of PEEK to bone.

This section focuses on strategies to improve the binding efficiency of PEEK with bone as well as cell and in vivo studies to provide a theoretical basis for its future application in implants.

2.1. Optimizing surface micromorphology and coarsening

The surface morphology and roughness of an implant are closely related to the implant treatment and are critical factors that affect the initial stability of the implant, level of marginal bone, and load-bearing capacity of the bone after implantation[34,35]. Therefore, optimizing the surface micromorphology and applying an appropriate roughness treatment can improve the binding efficiency of PEEK with bone.

Bone is schematically composed of a dense area (cortical layer) and a porous area (cancellous bone) containing structures on many levels, including micron, submicron, and nano[36]. Based on the principle of bionics, an implant surface with a micro/nano structure is conducive to the adhesion, proliferation, differentiation, and integration of bone cells[37]. Xu et al.[38] used a combination of oxygen plasma injection and sandblasting technologies to generate a micro/nano-morphological structure on the PEEK surface. The micro/nano morphological structure promoted adhesion, proliferation, and mineralization of the human osteoblast-like MG-63 cells. In in vivo experiments, PEEK on micro-nano surfaces had a higher level of mechanical interlocking and bone-binding strength. Therefore, optimizing the PEEK surface micromorphology is an excellent strategy to improve its binding efficiency with bone.

Appropriate surface roughness has been proven to increase the biomechanical strength of the implant–bone interface and promote osseointegration. An implant with a rough surface has stronger anti-rotation, anti-tension, and anti-compression stability than an implant with a smooth surface[39–41], which is important for the long-term stability of implants in bone. The surface of PEEK is relatively smooth, and many researchers have attempted to increase its surface roughness to enhance its biological activity. Mahrous et al.[42] treated PEEK with atmospheric plasma spraying and increased its surface roughness. In vivo, the results showed that the plasma-sprayed PEEK implant had a higher percentage of bone-implant contact than untreated PEEK. Khoury et al.[43] used accelerated neutral atom beam technology (ANAB) to modify the surface of PEEK to form ANAB-PEEK, and the average roughness (Ra) increased significantly. Compared with PEEK, the binding strength between ANAB-PEEK and sheep hindlimb bone increased by 3.09 times, indicating that proper surface roughness treatment of PEEK is an effective strategy to improve its binding efficiency with bone.

Osseointegration can be promoted by a micron/nano structure that simulates natural bone tissue and appropriate surface roughness. However, it is challenging to obtain an accurate and controllable micron/nano surface and to identify the optimal microscopic morphology conducive to PEEK osteogenesis. In addition, there is currently no uniform standard for optimal roughness evaluation. Finally, the increase in material surface roughness promotes the adhesion and growth of bacteria, which can easily cause peri-implantitis. These are the problems facing optimization of the surface micromorphology and coarsening of PEEK.

Table 2. List of current surface modification strategies to improve the tissue integration of polyetheretherketone (PEEK)

Object	Current Surface Modification Strategies	Active Factors	Technologies and Methods	Notable Effects	Ref
Improving the Binding Efficiency of PEEK with Bone	optimizing surface micromorphology and coarsening	micro/nano surface increased roughness	oxygen plasma injection and sandblasting atmospheric plasma spraying; ANAB technology	promoted the adhesion, proliferation and mineralization of MG-63 cells and improved bone-binding strength	[38] [42][43]
	coating bioactive materials	HA Ti and TiO_2 PDA graphene	IBAD technology; high temperature melting surface activation and vacuum plasma spraying; not mentioned self-polymerization of dopamine chemical vapor deposition	improved the interface shear strength between femoral bones and CFR/PEEK; increased the new bone formation, bony apposition, and pullout strength; maintained better endplate bone fusion; enhanced the activity of BMSCs and the upregulation of osteogenic-related gene expression	[45][46] [49][50] [52][53] [56]
	grafting chemical groups	sulfonic acid groups phosphate group amino groups	sulfonation technology diazotization reaction; two-step chemical reaction chemical vapor deposition technology	improved protein absorption and apatite formation capacity; improved the deposition rate of bone-like apatite and enhanced the bone integration ability; increased the activity of MSCs and improved the bone–implant contact rate and binding strength	[60][61] [62][63] [64]
	incorporating trace elements	Zn Mg Sr Si	plasma-induced graft polymerization microwave energy compression molding technique electron beam evaporation	promoted the proliferation of MC3T3-E1 cells and increased the gene expression levels of ALP, OCN, and BSP; promote the formation of new bone; enhanced the activity of rBMSCs-OVX and osseointegration	[67] [70] [73] [76]
	introducing bioactive molecules	BMP-2 RGD OGP	freeze-drying technology cross-linking agent-mediated peptide immobilization bioorthogonally clicked	enhanced the activity of rBMSCs; promoted the proliferation, differentiation and formation of bone-like apatite of osteoblasts; improved the binding efficiency of PEEK with bone under infection conditions	[80][81] [83][84] [86]
	appropriately improving surface hydrophilicity	increased hydrophilicity	UV irradiation; oxygen/ammonia plasma	decreased CA	[90][91] [92]
Improving the Binding Efficiency of PEEK with Soft Tissue	forming a porous surface	porous surface	sulfonation; acid-etched	promoted the adhesion of newly regenerated soft tissues and formed a tight implant–tissue interface; promoted the adhesion of human fibroblasts, and improved the ability to form a mechanical bond with soft tissues	[99] [100]
	application of bioactive nanocoating	TiO_2 nanocoating TP nanocoating ST coating	plasma immersion ion implantation vacuum evaporation hydrothermal method	regulated the migration and proliferation of cells and the formation of focal adhesion of HGFs and HGEs	[103] [104] [105]
	appropriately improving surface hydrophilicity	increased hydrophilicity	laser and plasma treatment; chemical modification	improved the adhesion ability of HGFs; enhanced the hydrophilicity and protein affinity of PEEK; had stronger cell adhesion and faster soft tissue growth	[108] [109]
	innovative surface cleaning methods	clean and active surface	surface active cleaner Decon solution	resulted in a higher HGF survival rate	[112]

2.2. Coating bioactive materials

Surface modification of PEEK with bioactive coatings is a promising approach for imparting bioactivity. Bone formation on the implant surface is directly affected by the quality of the surface coating and interactions between the coating material and osteoblasts.

2.2.1. HA

HA is an essential inorganic component present in bone that can promote the growth of new bone through osteoconductive mechanisms[44]. Durham et al.[45] used ion beam-assisted deposition technology to deposit HA and yttria-stabilized zirconia (YSZ) coatings on the surface of PEEK implants and implanted them into the femurs of rabbits. Compared to uncoated PEEK, PEEK with HA/YSZ coating had a better implant fixation effect, higher bone regeneration, and a larger bone–implant contact area. Nakahara et al.[46] coated HA particles on the surface of CFR/PEEK, significantly improving the shear strength of the interface between the femoral bones and CFR/PEEK in rabbits.

2.2.2. Ti and TiO2

Ti has good biocompatibility and bone-conduction properties. Using Ti to coat the surface of PEEK can not only improve its biological activity, but also maintain its elastic modulus[47]. Ti is prone to oxidation reaction under natural conditions, and the compound titanium dioxide (TiO_2) also shows good biocompatibility. Therefore, many researchers have used Ti or TiO_2 coatings on PEEK to improve its binding efficiency with bones[48]. Cheng et al.[49] used surface activation and vacuum plasma spraying techniques to coat PEEK surfaces with Ti. In an in vivo sheep model, new bone formation, bony apposition, and pullout strength of Ti-PEEK implants increased significantly compared to PEEK without Ti. Hasegawa et al.[50] randomly allocated patients undergoing posterior lumbar interbody fusion (PLIF) surgery to receive either TiPEEK or PEEK cages. Six months after surgery, the TiPEEK cage in PLIF maintained a better endplate bone fusion than the PEEK cage.

2.2.3. Polydopamine (PDA)

PDA is rich in catechol groups and amino functional groups of lysine and has excellent adhesion properties[51]. Coating the PEEK surface with PDA improves its biocompatibility. Wang et al.[52] successfully coated a PEEK surface with PDA via self-polymerization of dopamine. In vitro experiments indicated that PDA coating considerably enhanced the activity of rat bone marrow mesenchymal stem cells (rBMSCs) and upregulated osteogenic-related gene expression. An in vivo study confirmed that PDA coating remarkably accelerated new bone formation and enhanced osseointegration. Zhang et al.[53] assessed the effect of a lithium-doped silica nanosphere/PDA composite (LPC) coating on PEEK bioactivity. The modification significantly promoted the mineralization of apatite in simulated body fluid (SBF) and stimulated the reaction of rBMSCs. In vivo experiments showed that the bone tissue around the modified PEEK reacted more actively and had a higher osseointegration efficiency than unmodified PEEK.

2.2.4. Graphene

Graphene has a two-dimensional crystal structure composed of carbon atoms, according to the SP2 hybrid orbits. Its basic structural unit is a six-membered carbon ring, which is the basic module of other dimensional graphite materials[54]. Graphene has excellent mechanical properties and can promote the adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 cells in artificial ligaments[55]. Yan et al.[56] successfully used chemical vapor deposition and $FeCl_3$ etching to coat the surface of CFR-PEEK with graphene. Experiments have shown that graphene modification significantly promotes the activity of bone marrow stromal cells and new bone formation in rabbits. This suggests that graphene may have considerable potential for enhancing the binding efficiency of PEEK with bone.

Coating bioactive materials can improve the binding efficiency between PEEK and bone. However, it remains inconclusive whether the binding strength between the coating and PEEK can meet the requirements of implants for long-term use in vivo. In addition, such modification technologies as vapor deposition are constrained by "line of sight," which makes it difficult to process the biomedical implants of complex shapes. Therefore, it is imperative to determine how coatings with uniform thickness, density, and strong binding strength can be prepared on PEEK surfaces of different shapes.

2.3. Grafting chemical groups

The surface chemical properties of biomaterials have an essential influence on the adsorption of proteins, such as fibronectin, integrin, paxillin, and actin, in vivo, and can regulate cellular responses on the surface, thus affecting healing at the interface between an implant and the surrounding tissue[57]. PEEK has an extremely high chemical stability, but Noiset et al.[58] found that the carbonyl group in benzophenone on its molecular chain can form a hydroxyl group under the action of an initiator, and the hydroxyl group can be used to graft functional groups to further chemically modify the PEEK surface. The properties of PEEK can be improved by introducing corresponding active functional groups, such as sulfur, amino, and phosphoric groups, on the surface by chemical treatment, light irradiation, or plasma treatment.

The sulfate group carries a negative charge and can attract positively charged Ca^{2+} ions to promote osteogenic transformation. In addition, the negatively charged surface is more attractive for cell adhesion proteins, and moderate sulfur-containing compounds have disinfectant properties that can prevent infection and improve the success rate of implant surgery[59]. Li et al.[60] introduced sulfonic acid groups on the PEEK surface through sulfonation and then hydrothermally treated the specimens. This modification promoted the activity of BMSCs and significantly increased the binding efficiency of PEEK to the bone. Wan et al.[61] modified PEEK by controlling the sulfonation of sulfur trioxide (SO_3). With increased sulfonation, the protein absorption and apatite formation capacity improved. Moreover, the activity of MC3T3-E1 cells on the PEEK surface was enhanced after sulfonation.

The phosphate group is an essential component of human bone, and phosphorylation of implant surfaces is beneficial for bone regeneration, which has received extensive attention from researchers. For example, Mahjoubi et al.[62] grafted phosphonate groups onto PEEK chains through a diazotization reaction, which improved the deposition rate of bone-like apatite during SBF soaking. In addition, in vivo experiments in rats suggested that the phosphonate group could significantly enhance the bone integration ability of PEEK implants. Fukuda et al.[63] roughened the PEEK surface by sandblasting and phosphorylated it through a two-step chemical reaction. Surface roughening did not improve the response of rat mesenchymal cells (MSCs). However, the phosphorylation of smooth substrates increases the activity of MSCs. In addition, in an implanted rabbit tibia model, the combination of PEEK surface roughening and phosphorylation modification significantly improved the bone–implant contact rate and binding strength after implantation.

Proteins and many carbohydrate compounds contain amino groups that have a high affinity for body tissues. In addition, studies have shown that fibronectin in the extracellular matrix plays a significant role in the process of osteoblast adhesion; the main integrin binding domain RGD sequence in fibronectin is extremely sensitive to $-NH_2$ on the surface of the material, which in turn modulates the integrin-mediated signaling pathways to enhance cell adhesion, spreading, proliferation, and differentiation[57]. Yu et al.[64] successfully introduced amino groups onto the surface of PEEK using chemical vapor deposition and significantly improved the hydrophilicity and osteogenic properties.

The grafting of chemical groups facilitates the attachment of bioactive molecules and osteoblasts, which is conducive to improving the biological activity of PEEK. However, the stability of the active group is essential for chemical modification. When the group detaches from the implant surface, the local pH level of the microenvironment may differ from the normal range, which negatively affects the surrounding cells and tissues. Through controlled binding of bioactive groups, grafting can induce bone integration. However, this method involves a complex process and it is difficult to release fixed molecules directly. As a result, the duration of the biological activity is limited. Maintaining the stability and activity of the key groups remains a challenge.

2.4. Incorporating trace elements

Besides macro elements, such as calcium (Ca) and phosphorus (P), bone also contains trace elements, such as zinc (Zn), magnesium (Mg), strontium (Sr), and silicon (Si), which are essential for growth and development[65]. Therefore, the osseointegration of an implant

can be promoted by incorporating osteogenic elements into its surface. In the following section, we introduce the trace elements that researchers have incorporated on the surface of PEEK and the corresponding methods to improve the binding efficiency of PEEK with bone.

2.4.1. Zn

Zn is not only closely related to the growth and development of human bone but is also an indispensable part of the formation of critical enzymes such as ALP and the normal function of catalytic regulation in the process of bone formation in the human body[66]. Zhang et al.[67] constructed an acrylic polymer coating loaded with Zn^{2+} on the PEEK surface by combining plasma-induced graft polymerization and chemical impregnation. Successful coating significantly promoted the proliferation of MC3T3-E1 cells and increased the gene expression of ALP, osteocalcin (OCN), and bone salivating protein (BSP).

2.4.2. Mg

Mg has attracted much attention in bone tissue engineering because of its indirect effects on bone matrix and mineral metabolism[68]. Artificial bone materials mixed with Mg showed good osteogenic properties when used to repair bone defects[69]. Ren et al.[70] used microwave energy to form an amorphous magnesium phosphate (AMP) coating on a PEEK surface. The results showed that AMP coating was beneficial for the adhesion and proliferation of MC3T3-E1 cells in the early stage. Furthermore, the high OCN expression in cells cultured on AMP-PEEK samples suggests that AMP coating can promote the formation of new bone on the PEEK surface and improve its binding efficiency with bone.

2.4.3. Sr

Sr promotes osteoblast proliferation and inhibits osteoclast proliferation In addition, Sr can replace a small amount of Ca in HA crystals of calcified bone and tooth tissue and improve the mechanical properties of bones[71,72]. Wong et al.[73] introduced Sr-containing HA (Sr-HA) into PEEK to prepare Sr-HA/PEEK. The MG-63 cell experiment results proved that Sr-HA/PEEK was superior to HA/PEEK in terms of biological activity, and Sr has been shown to enhance the osteogenic activity of PEEK.

2.4.4. Si

Si facilitates cartilage formation and plays a vital role in mineralization. In the early stages of the biomineralization process, Si can be found in the more active parts of the calcification[74,75]. Wen et al.[76] used electron beam evaporation (EBE) technology to introduce active Si coatings onto PEEK by precisely adjusting the amount of Si. Compared with PEEK, the activity of rBMSCs-OVX was significantly enhanced on silicon-containing PEEK. In particular, better osseointegration in vivo was observed in PEEK coated with the highest silicon content group than other groups.

Incorporating trace elements into the surface of PEEK is an effective solution to promote osseointegration and has promising prospects. However, it is worthwhile to pay attention to the amount of trace elements released into the body and whether it can have a positive impact on a certain level, especially metal elements, if the excess is bound to be toxic to the body. In the future, a further research shall be conducted on the osteogenic mechanisms of these trace elements, so as to better understand how they affect bone healing and growth.

2.5. Introducing bioactive molecules

Bioactive molecules, such as bioactive proteins and molecular peptides, are fixed on the surface of implants in a certain way to promote the formation of peri-implant bone and improve implant osseointegration through osteogenic induction[77]. Biomolecules promote the proliferation and differentiation of osteoblasts, which are more direct and effective than traditional physical and chemical methods[78]. Combining such biomolecules with PEEK implants and giving full play to their activity is a central problem of current research.

2.5.1. Bone morphogenic proteins-2 (BMP-2)

BMP-2 can positively regulate bone tissue regeneration and repair processes and induce osteogenic differentiation in in vitro cell systems[79]. In recent years, BMP-2 has been used for surface modification and satisfactory results have been achieved. Senatov et al.[80] introduced recombinant BMP-2 into HA/PEEK and implanted it into the rat skull. Compared with the HA/PEEK group, the loading of BMP-2 led to a significant increase in the amount of bone tissue in the implanted area of the rat skull. Sun et al.[81] adopted freeze-drying technology to immobilize BMP-2 on sulfonated PEEK (SPEEK), and the three-dimensional network structure of SPEEK enabled the release of BMP-2 in a controlled and sustained manner. Cell experiments showed that BMP-2 immobilization significantly enhanced the activity of rBMSCs on SPEEK.

2.5.2. Arginine–glycine–aspartic acid (RGD)

RGD has a short peptide sequence that cells recognize and bind to in an extracellular matrix, such as osteopontin or fibronectin. Postoperatively, RGD can significantly improve cell adhesion and accelerate osseointegration around the implant, which is conducive to better initial implant stability. RGD can play a positive role in the bone-tissue interface of implants[82]. Becker et al.[83] used fatty diamines to form Schiff bases, followed by cross-linking agent-mediated peptide immobilization to modify the PEEK surface. In a cell culture experiment using primary human osteoblasts isolated from the femoral heads of healthy donors, RGD-modified PEEK was found to significantly promote cell adhesion. Zhu et al.[84] implanted RGD on a PEEK surface using a PDA bonding platform. Cell experiments showed that RGD modification promoted proliferation, differentiation, and formation of bone-like apatite of osteoblasts on the PEEK surface.

2.5.3. Osteogenic growth peptide (OGP)

OGP, a polypeptide composed of 14 amino acids, promotes a systemic response to bone marrow injury. OGP stimulates the activity of osteoblasts, promotes the growth of osteoblasts and fibroblasts, and promotes a secondary hematopoietic response caused by the stimulation of the matrix microenvironment. Thus, OGP plays a key role in the treatment of osteoporosis and hematological diseases[85]. Li et al.[86] bioorthogonally clicked antimicrobial peptides and OGP on PEEK using the binding of mussel foot protein-mimic peptide and the addition reaction of its azido terminal with dibenzylcyclooctyne to achieve dual host defense and tissue repair effects. Bioorthogonal

clicks can accurately match the antimicrobial peptide and OGP by changing the molar ratio; thus, this study improved the binding efficiency of PEEK with bone under infection conditions.

Bioactive molecules play a crucial role in promoting the formation of new bone and increasing the initial stability of implants. However, because most bioactive molecules are derived from tissues and recombinantly produced, the level of biological activity could vary between different batches. Additionally, the presence of donor material residues poses a risk of infection and immunogenicity. In addition, bioactive molecules are enzymatically degradable, which is detrimental for maintaining long-term biological activity. Therefore, further research is required to ensure the safe and stable release of biomolecules from the surface of implants for clinical applications.

2.6. Appropriately improving the surface hydrophilicity

A hydrophilic implant surface is more conducive to the deposition of blood clots and fibrin; furthermore, by promoting the early adhesion of osteoblasts, it stimulates rapid initiation of the biological stability healing stage[87]. In addition, a hydrophilic implant surface can inhibit cell differentiation into osteoclasts, and this effect may be beneficial for slowing down the loss of bone around an implant and ensuring long-term stability[88]. The untreated PEEK surface is hydrophobic, and improving its hydrophilicity may be crucial for its clinical use[89]. UV radiation and plasma technology can effectively improve the hydrophilicity of PEEK. Qahtani et al.[90] irradiated PEEK implants with UV-A and UV-C. Dynamic contact angle (CA) analysis showed that the unexposed implants were hydrophobic and the exposed implants were hydrophilic. Naauman et al.[91] found that the higher the oxygen content of the PEEK surface under UV irradiation, the more pronounced the effect of improving hydrophilicity, and concluded that UV-C could induce hydrophilicity better than UV-A. Waser-Althaus et al.[92] treated PEEK with an oxygen/ammonia plasma. Static CA measurements showed that the hydrophilicity of the treated PEEK surface increased. Simultaneously, the increased oxygen plasma power led to a decrease in CA.

Thus, improving the hydrophilicity of PEEK can promote osseointegration. However, the current hydrophilic modification technologies still have some limitations. For example, implants exposed to air for too long are susceptible to contamination and show suppressed hydrophilic activity. Additionally, whether modified implants can remain hydrophilic after exposure to high temperatures and ultraviolet (UV) disinfection is debatable. To solve this concern, it is worthwhile to explore an effective strategy to design a PEEK implant that can maintain hydrophilicity for a long period.

2.7. Chapter summary

Modification of the surface morphology and material coating, introduction of active chemical components, biochemical modification, and enhancement of hydrophilicity are crucial for improving the bone-binding efficiency of PEEK surfaces. Nevertheless, these strategies are not perfect and existing research mainly consists of in vitro or short-term in vivo experiments; therefore, evaluating the osseointegration of modified PEEK requires extensive long-term in vivo experiments based on optimizing the existing modification methods.

3. Strategies for improving the binding efficiency of PEEK with soft tissues

Superior adhesion of the soft tissue around the implant can act as a biological barrier to protect the stability of the implant and the bone tissue interface, leading to the long-term success of the implant[93]. Peri-implant soft tissue sealing relies not only on epithelial attachment, but more importantly, on the reconstruction of the fibrous connective tissue attachment to firmly support the epithelial barrier to prevent peri-implant inflammation and maintain the long-term success of implants[94]. The fibrous connective tissue around the implant is mainly composed of collagen fibers, cells, blood vessels, and extracellular matrix, with human gingival fibroblasts (HGFs) as the main components[95]. The number and activity of HGFs at the implant–mucosa interface profoundly impact the formation of soft tissue closure around the implant. There are few reports on improving the binding efficiency of PEEK implants with soft tissues, and this section describes those improvement strategies.

3.1. Forming a porous surface

Because PEEK with a smooth surface can easily lead to fibrous encapsulation, creating a microporous surface morphology is a strategy to improve its binding efficiency with soft tissue by simulating the trabecular structure of natural bone[96,97]. Meanwhile, a microporous surface can more effectively establish extensive and close connections with soft connective tissue in the early healing stage, promoting stable long-term fusion with soft tissue and thus improving the healing and tissue regeneration effects of implants[98]. Su et al.[99] formed a uniform microporous structure on a PEEK lattice scaffold via sulfonation, and experiments with rabbits showed that sulfonated micropores promoted the adhesion of newly regenerated soft tissues and formed a tight implant–tissue interface. Feng et al.[100] showed that an acid-etched microporous surface promoted the adhesion of human fibroblasts, and the internal cross-linked structure improved the ability of PEEK to form a mechanical bond with soft tissues, indicating its potential for clinical applications.

The porous surface expands the space available for the adhesion and growth of gingival cells, which enhances the binding efficiency between PEEK and soft tissue. However, it is difficult to achieve an ideal porosity. The formation of a porous surface inevitably reduces the mechanical strength of the surface, and there are still no stress analysis experiments conducted in vivo. In addition, it is difficult to achieve the desired precision because of the small pore size and high porosity.

3.2. Application of bioactive nanocoating

Biomaterials with surface nanostructures can provide binding sites for cells, which is conducive to cell adhesion, diffusion, and growth[101]. In addition, an abutment with a nanomorphological surface can promote early attachment and proliferation of HGFs in a predetermined manner, promote the secretion of collagen fiber bundles perpendicular to the oral surface, and provide a tight seal against the invasion of oral pathogens[102]. Therefore, in theory, constructing a bioactive nanocoating on the PEEK surface can improve its binding efficiency with soft tissues. Wang et al.[103] applied Ti plasma immersion ion implantation technology to modify the surface of carbon-fiber-reinforced PEEK and constructed a unique multilayer TiO_2 nanostructure. After analysis, it was concluded that the nanoscale surface significantly affected the synthesis of the

extracellular matrix and regulated the expression of integrin, thus directly regulating the migration and proliferation of cells and the formation of focal adhesion of HGFs. Pang et al.[104] successfully prepared a dense coating of tantalum pentoxide combined with PEEK (PKTP) using vacuum evaporation and examined the reaction of human gingival epithelial (HGE) cells with PKTP and PEEK. Compared to PEEK, the adhesion and proliferation of HGE cells on the surface of PKTP were significantly improved. Ren et al.[105] synthesized nano cubic sodium tantalate (ST) particles using a hydrothermal method and prepared ST and PEEK composite (TPC) materials. The results showed that the ST content in TPC significantly affected the surface properties and played a crucial role in stimulating the HGE-1 cell response.

At present, bioactive nanocoatings are widely adopted for research on implant surface modification owing to their unique advantages, such as small size and interfacial effects. However, the use of nanocoatings is potentially detrimental. After being released into the blood, nanoparticles can penetrate into the blood–brain barrier and enter the central nervous system. Currently, the clinical application of nanomaterial-coated implants is increasing rapidly. Therefore, it is necessary to verify the long-term safety and standardize these nanocoating by continuously improving their manufacturing process.

3.3. Appropriately improving the surface hydrophilicity

Surfaces with different wettabilities will lead to differences in the number and shape of the attached cells, and the surface of hydrophilic materials is more conducive to early cell adhesion and spreading[106]. In addition, with a hydrophilic surface, blood and proteins can rapidly attach, which is further demonstrated at the tissue level by good soft tissue integration, tight interface, and less interface space, thus accelerating tissue binding around the implant[107]. The hydrophilicity of the implant can affect its binding efficiency with the surrounding tissues. Therefore, appropriately improving the surface hydrophilicity of the material can promote its binding with soft tissues. Gheisarifa et al.[108] reported the adhesion ability of HGFs on the surfaces of different implant abutment materials, and showed that the hydrophilicity of PEEK modified by laser and plasma treatments was significantly improved. After seven days of cell proliferation, the number of cells on the surface of the modified PEEK was significantly higher than that on the unmodified PEEK and Ti alloy. Liu et al.[109] connected 3-aminopropyl triethoxysilane to a 3D printed PEEK surface via chemical modification. Uniform amino groups on the amidogen interface significantly enhanced the hydrophilicity and protein affinity of PEEK. In addition, the modified PEEK surface exhibited stronger cell adhesion and faster soft tissue growth than the unmodified PEEK.

By improving the hydrophilicity of PEEK, its interactions with gingival cells can be enhanced. However, implants with active groups can be subjected to friction during placement. Otherwise, there would be changes in the surface morphology and chemical composition to improve PEEK hydrophilicity. As a result, it is difficult to explore the effect of hydrophilicity on the soft tissue-sealing function of PEEK.

3.4. Innovative surface cleaning methods

Contamination of the implant surface can affect the cell growth. Cleaning the surface of the implant abutment is crucial for decontamination and can change the surface properties, thereby altering the cell response[110]. A reasonable cleaning method can reduce the debris on implant abutment, avoid irritation to the soft tissue, and promote soft tissue healing[111]. Therefore, optimizing the method for cleaning the PEEK surface can promote its combination with soft tissues.

Rutkunas et al.[112] used Decon solution (Decon 90; Fisher Scientific, Hampton, NH, USA), a laboratory-grade alkaline surface-active cleaner, to develop a multi-step research cleaning protocol (RCP). Compared with the traditional ultrasonic cleaning method, this RCP reduced the surface roughness and increased the CA of the polymethylmethacrylate, PEEK, and polyetherketoneketone polymer materials. In a cell experiment, RCP resulted in a higher HGF survival rate on polymer surfaces after 48 h, indicating that cleaning methods with different polymer materials can affect the surface properties and HGF activity, thereby affecting the binding efficiency of PEEK with soft tissues.

Surface cleaning plays an important role in implant surface modification. Currently, commonly used clinical methods are limited to mechanical, ultrasonic, and ultraviolet disinfection. Therefore, the development of a low-cost, safe, and effective cleaning method can provide a new strategy for implant surface decontamination, which is an excellent choice for the combination of multiple cleaning programs.

3.5. Chapter summary

The relationship between the implant and soft tissue is important for implant treatment, but there are relatively few studies on improving the binding efficiency of PEEK with soft tissues. The main strategies include fabricating porous surfaces and nanocoatings, improving the hydrophilicity of the surface, and cleaning the surface. Further research is necessary to provide an experimental and theoretical basis for the future application of PEEK implants and abutment materials for soft tissue repair.

4. Future research direction

The strategies proposed in Chapters 2 and 3 to improve the binding efficiency of PEEK with bone and soft tissues provide references for future PEEK modification research. According to a comprehensive analysis, each strategy has its strength, and there are possible directions for research to refine these existing modification methods. For example, 3D printing and laser engraving can provide technical support for obtaining precise and controllable micro/nano surface micromorphology and roughness. Second, stable and uniform coatings can be constructed on the PEEK surface by expanding the area of contact between PEEK and bioactive materials with acid etching and sandblasting, and by optimizing the coating technology. In addition, to prevent the burst effect of bioactive molecules, sustained-release carriers, such as microspheres and layer-by-layer self-assembly systems, can be used to achieve effective controlled release of bioactive molecules. In addition, the synergistic effects of different trace elements can promote implant integration. However, further experiments are required to determine the optimal concentrations and long-term biological toxicity. Furthermore, dentists can rely on UV irradiation chairside treatment of PEEK implants to improve their hydrophilicity. Finally, compared with a single surface modification method, a combination of multiple strategies, such as changing the chemical composition after optimizing the surface structure and introducing ions and molecules after coating, can produce a more

significant effect on the surface modification of PEEK.

In addition to the strategies used to improve the binding efficiency of PEEK with bone and soft tissues, future research should also be conducted for the widespread use of PEEK as a dental implant material in clinical treatment, with special focus on the following points:

- To optimize the antibacterial properties of PEEK implants.
- To explore the molecular mechanisms and proteins and signaling pathways expressed in the early stages of PEEK implantation.
- To study the all-around performance of PEEK in complex physiological environments, such as the human body or the area close to the human body, to reveal its response at each stage of implantation.
- To determine the stability of the implant under disease conditions, such as osteoporosis and diabetes.

5. Conclusions

PEEK has great potential as a dental implant material owing to its superior performance, and has been widely studied in the fields of biomedicine and material science. Although many studies have shown that various surface modifications can successfully improve the biological activity of PEEK, most of these studies were based on in vitro or short-term in vivo evaluations. To achieve broad application of PEEK in oral implants, more in vivo experiments and long-term clinical evaluations are needed to investigate the effects of various surface modifications on the tissue integration ability of PEEK implants.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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